AMENDMENTS TO THE SPECIFICATION

Please amend the paragraph on page 2, line 2 as follows:

The present application claims priority to co-pending U.S. Application Serial No. 09/310,802, filed May 12, 1999, now abandoned, which claims priority to second provisional application Serial No. 60/109,054, filed November 19, 1998 and to first provisional application Serial No. 60/085,305, filed May 13, 1998; the entire specifications, claims and figures of which application and provisional applications are incorporated herein by reference without disclaimer. The U.S. Government owns rights in the present invention pursuant to Grant Numbers 1RO1DE13004, DE07057 and AR40673 from the National Institutes of Health.

Please amend the paragraph on page 2, line 10 as follows:

Also specifically incorporated herein by reference without disclaimer are U.S. Patent Application Serial No. 09/402,119, filed September 20, 1999, now U.S. Patent No. 6,281,256 which claims priority to PCT Application No. PCT/US98/06188 (WO 98/44027), filed March 31, 1998, which designated the United States and which claims priority to U.S. Provisional Application Serial No. 60/042,198, filed March 31, 1997; and PCT Application No. PCT/US97/16890 (WO 98/12228), filed September 19, 1997, which designates the United States and which claims priority to U.S. Provisional Applications Serial Nos. 60/026,362, 60/026,467 and 60/041,565, filed September 19, 1996, September 19, 1996 and March 21, 1997, respectively. Applicants expressly reserve the right to claim priority to one or more of the foregoing incorporated applications.

Please amend the paragraph on page 20, line 29 as follows:

The preparation and use of porous hydrogel materials formed by first creating gas pockets in the gel and then removing the gas to create a material with an open, interconnected pore structure is also included. Such matrices maintained their pore structure over extended time periods and have high mechanical integrity. U.S. Provisional Application Serial No. 60/128,681, filed April 09, 1999, the priority document for U.S. Patent No. 6,511,650, is specifically incorporated herein by reference without disclaimer for the purposes of describing the preparation and use of such unique polymeric materials and matrices thereof.

Please amend the paragraph on page 30, line 8 as follows:

The entire specification, claims, figures and sequence listings of the following patent applications are specifically incorporated herein by reference without disclaimer: provisional application Serial No. 60/085,305, filed May 13, 1998; provisional application Serial No. 60/109,054, filed November 19, 1998; U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416; U.S. Application Serial No. 08/316,650, filed September 30, 1994, now U.S. Patent No. 5,942,496; U.S. Application Serial No. 08/479,722, filed June 07, 1995, now U.S. Patent No. 6,074,840; U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 6,143,037; PCT Application Serial No. PCT/US97/07301, filed April 11, 1997 (WO 97/38729); U.S. Application Serial No. 08/662,341, filed June 12, 1996, now U.S. Patent No. 6,143,037; PCT Application Serial No. PCT/US97/10079, filed June 11, 1997 (WO 97/47254); U.S. Application Serial No. 08/752,919, filed November 20, 1996, now abandoned; PCT Application Serial No. PCT/US97/20882, filed November 20, 1997 (WO 98/22492); U.S. Patent Application Serial No. 09/402,119, filed September 20, 1999, now U.S. Patent No. 6,281,256; PCT Application Serial No. PCT/US98/06188, filed March 31, 1998 (WO 98/44027), which designates the United States; U.S. Provisional Application Serial No. 60/042,198, filed March 31, 1997, the priority document for U.S. Patent Nos. 6,281,256 and 6,797,738 and WO 98/44027; U.S. Provisional Application Serial No. 60/026,362, filed September 19, 1996, the priority document for U.S. Patent No. 6,642,363; U.S. Provisional Application Serial No. 60/026,467, filed September 19, 1996, the priority document for U.S. Patent No. 6,642,363; U.S. Provisional Application Serial No. 60/041,565, filed March 21, 1997, the priority document for U.S. Patent No. 6,642,363; PCT Application Serial PCT/US97/16890, filed September 19, 1997 (WO 98/12228); U.S. Provisional Application Serial No. 60/066,926, filed November 17, 1997, the priority document to U.S. Application Serial No. 09/572,786, now abandoned; and U.S. Provisional Application Serial No. 60/128,681, the priority document for U.S. Patent No. 6,511,650, filed April 09, 1999. Applicants expressly reserve the right to claim priority to any one or more, or all of, the foregoing patent applications.

Please amend the paragraph on page 36, line 28 as follows:

The preferred processes for matrix generation are thus termed "GF/PL processes" (gas foaming/particulate leaching processes), as opposed to the less adequate solvent-

casting/particulate leaching (SC/PL) processes used prior to the invention. The entire text and figures of U.S. Patent Application Serial No. 09/402,119, filed September 20, 1999, now U.S. Patent No. 6,281,256, PCT Application No. PCT/US98/06188 (WO 98/44027), filed March 31, 1998, which designates the United States, and U.S. Provisional Application Serial No. 60/042,198, filed March 31, 1997, the priority document for U.S. Patent Nos. 6,281,256 and 6,797,738 and WO 98/44027, are also each specifically incorporated herein by reference without disclaimer for the purposes of even more fully describing matrix generation using GF/PL processes.

Please amend the paragraph on page 45, line 1 as follows:

The reduction in molecular weight can be effected by hydrolysis under acidic conditions or by oxidation, to provide the desired molecular weight. Hydrolysis can be conducted to result in a sodium poly(guluronate) of lower molecular weight that is essentially absent of mannuronic acid units. The oxidation to lower molecular weight is preferably conducted with a periodate oxidation agent, particularly sodium periodate (PCT/US97/16890, WO 98/12228).

Please amend the paragraph on page 51, line 4 as follows:

Exemplary tissue specific promoter/enhancer elements and transcriptional control regions that exhibit tissue specificity include, but are not limited to: the elastase I gene control region that is active in pancreatic acinar cells; the insulin gene control region that is active in pancreatic β cells; the immunoglobulin gene control region that is active in lymphoid cells; the albumin, αl-antitrypsin and α-fetoprotein gene control regions that are active in liver; the β-globin gene control region that is active in myeloid cells; the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain; the myosin light chain-2 gene control region that is active in skeletal muscle; and the gonadotropic releasing hormone gene control region that is active in the hypothalamus. U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 5,962,427 and PCT Application Serial No. PCT/US97/07301, filed April 11, 1997, (WO 97/38729), are both incorporated herein by reference for the purposes of incorporating references even further describing the foregoing elements.

Please amend the paragraph on page 56, line 1 as follows:

U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416; U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 5,962,427; and PCT Application Serial No. PCT/US97/07301, filed April 11, 1997, (WO 97/38729); each incorporated herein by reference, describe applications of the invention to *in vivo* methods for targeting and transfer of DNA into mammalian repair cells.

Please amend the paragraph on page 58, line 13 as follows:

As described in U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416; U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 5,962,427; and PCT Application Serial No. PCT/US97/07301, filed April 11, 1997, (WO 97/38729); each incorporated herein by reference for this purpose, the present invention may be used in conjunction with one or more osteogenic or osteotropic genes.

Please amend the paragraph on page 83, line 27 as follows:

Bone has a substantial capacity to regenerate following fracture. Defects in the process of bone repair and regeneration are linked to the development of several human diseases and disorders, *e.g.*, osteoporosis and osteogenesis imperfecta. Failure of the bone repair mechanism is, of course, also associated with significant complications in clinical orthopaedic practice, for example, fibrous non-union following bone fracture, implant interface failures and large allograft failures. The lives of many individuals can now be improved by application of the present invention to stimulate and strengthen the fracture repair process. Indeed, DNA release from matrices in general has already been shown to be operative for gene transfer into bone progenitor cells and wound-healing fibroblasts *in vivo* (see, e.g., U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, and U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 5,962,427, each incorporated herein by reference).

Please amend the paragraph on page 93, line 20 as follows:

Numerous genes, preferably mammalian or human genes, may be used as wound-healing or osteogenic genes for use in the matrix-gene transfer technology of the present invention. U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, is incorporated herein by reference for purposes including incorporating the

text concerning the preparation and use of the active fragment of the human parathyroid hormone gene (hPTH1-34), expression vectors containing the hPTH1-34 gene and the use of the hPTH1-34 gene in gene transfer to promote wound-healing, as exemplified by new bone formation. Hendy *et al.* (1981) is also incorporated herein by reference for purposes including describing the DNA and amino acid sequences of hPTH1-34.

Please amend the paragraph on page 93, line 29 as follows:

U.S. Application Serial No. 08/199,780, now U.S. Patent No. 5,763,416, is also incorporated herein by reference for purposes including incorporating the text concerning the preparation and use of the mouse bone morphogenetic protein-4 (BMP-4) gene, expression vectors containing the BMP-4 gene and the use of the BMP-4 gene in gene transfer to promote wound-healing, as exemplified by new bone formation. The amino acid sequence encoded by the mouse BMP-4 transgene, including the tag, is represented by SEQ ID NO:1 in U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, incorporated herein by reference for purposes including the incorporation of the referenced sequence. The human sequence for BMP-4 is well known to those of skill in the art and has been deposited in Genbank.

Please amend the paragraph on page 94, line 15 as follows:

Each of U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416; U.S. Application Serial No. ~~08/~~08/316,650, filed September 30, 1994, now U.S. Patent No. 5,942,496; and U.S. Application Serial No. Serial No. 08/479,722, filed June 07, 1995, now U.S. Patent No. 6,074,840; are also incorporated herein by reference for the purposes of describing the preparation and use of further isolated novel fibrillin-like genes, particularly latent LTBP-2 and LTBP-3.

Please amend the paragraph on page 94, line 21 as follows:

For LTBP-2, the nucleotide sequence of SEQ ID NO:1 and the deduced amino acid sequence of SEQ ID NO:2 from U.S. Application Serial No. Serial No. 08/479,722, now U.S. Patent No. 6,074,840 are specifically incorporated herein by reference. For LTBP-3, the nucleotide sequence of SEQ ID NO:2 and the polypeptide sequence of SEQ ID NO:3 from U.S. Application Serial No. 08/316,650, now U.S. Patent No. 5,942,496 are specifically incorporated herein by reference, as are the nucleotide sequence of SEQ ID NO:3 and the

polypeptide sequence of SEQ ID NO:4 from U.S. Application Serial No. Serial No. 08/479,722, now U.S. Patent No. 6,074,840. The LTBP-3 protein in particular includes a signal peptide, and five structurally distinct regions (Region 1- Region 5), as described in U.S. Application Serial No. Serial No. 08/479,722, now U.S. Patent No. 6,074,840, incorporated herein by reference.

Please amend the paragraph on page 95, line 1 as follows:

U.S. Application Serial No. 08/752,919, filed November 20, 1996, now abandoned, is also incorporated herein by reference in entirety for purposes including describing the preparation and use of further isolated novel genes, particularly activins/inhibins, such as liver activins. U.S. Application Serial No. 08/752,919, now abandoned is particularly incorporated for its teachings concerning vertebrate activins expressed in the liver. Activin β_C and β_E subunit genes and proteins, and domains and fragments thereof, are described; as are other members of the liver activin subgroup; liver activin genomic regulatory elements that regulate the expression of liver activins; antisense sequences and ribozymes; host cell expression systems, including hepatocytes; liver activin proteins, fusion (chimeric) proteins, polypeptides and peptides; antibodies to liver activin proteins; diagnostic detection methods; transgenic animals that express a liver activin; recombinant knock-out animals that do not express liver activin(s); antagonists and agonists of the liver activins; methods of modulating liver activin gene expression activity to regulate cell growth and/or differentiation and to treat abnormalities related thereto, including intracorporeal and extracorporeal liver tissue growth and regeneration; and methods of promoting hematopoiesis, local and systemic bone growth and regeneration; and compounds that effect all such modulatory, growth and/or regenerative processes.

Please amend the paragraph on page 95, line 18 as follows:

In particular, the nucleotide sequence of FIG. 1 of U.S. Application Serial No. 08/752,919, now abandoned is specifically incorporated herein by reference, as is the amino acid sequence of the encoded protein, as shown in FIG. 2 of U.S. Application Serial No. 08/752,919, now abandoned.

Please amend the paragraph on page 95, line 22 as follows:

U.S. Application Serial No. 08/752,919, now abandoned is particularly incorporated by reference for the purposes of describing activin gene compositions and activin gene-matrix compositions, and methods of using such compositions in the regulation of cell growth and/or differentiation including, but not limited to, stimulating liver regeneration, bone growth and hematopoiesis.

Please amend the paragraph on page 95, line 29 as follows:

Suitable techniques for the detection of mRNA in tissue obtained from the site of wound healing, *e.g.*, the site of bone regeneration, are known to those of skill in the art. Such techniques are also detailed in U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, incorporated herein by reference for purposes including describing suitable mRNA detection techniques. Northern analyses may also be employed.

Please amend the paragraph on page 96, line 5 as follows:

mRNA detection techniques are useful for detecting expression of the transgene mRNA itself, and also in detecting the expression of hormones, growth factor receptors and other molecules in the tissues. For example, in order for a parathyroid hormone (PTH) transgene to function as an osteogenic agent, it is likely that there is a requirement for the PTH/PTHrP receptor to be expressed in the bone repair tissue itself. The presence of PTH/PTHrP receptor expression in osteotomy repair tissue has been demonstrated in the rat osteotomy model (U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, incorporated herein by reference for this purpose).

Please amend the paragraph on page 96, line 14 as follows:

Proteins expressed from the transgenes may also be detected immunohistochemically and by substrate utilization assays. U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, is also incorporated herein by reference for the purpose of describing suitable immunohistochemical and substrate utilization assays. Commercially available radioimmunoassay kits are also suitable for use in such protocols, and may detect the protein product of the transgene itself, or an epitope specifically added for

the purposes of immunohistochemical detection (*e.g.*, using a specific antibody that recognizes the HA epitope, Majmudar *et al.*, 1991).

Please amend the paragraph on page 97, line 10 as follows:

Aliquots of a fibrous collagen implant material were soaked in solutions of pure marker gene DNA. The implant materials were then placed in the osteotomy site, and their expression determined. As shown in U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, incorporated herein by reference for this purpose, both marker genes were successfully transferred and expressed, without any failures, as demonstrated by substrate utilization assays. Since mammalian cells do not normally synthesize either marker gene product, this provides direct evidence that osteotomy repair cells were transfected *in vivo* and then expressed the β-galactosidase and luciferase transgenes as a functional enzymes.

Please amend the paragraph on page 97, line 21 as follows:

In vivo gene transfer into regenerating bone was also achieved using matrix-adenovirus-mediated transfer. Adenovirus constructs may be prepared as described by Stratford-Perricaudet *et al.*, 1992, and Davidson *et al.*, 1993, each incorporated herein by reference. Successful adenoviral gene transfer of marker gene constructs into bone repair cells was demonstrated in the rat osteotomy model, and fully described in U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416; U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 5,962,427; and PCT Application Serial No. PCT/US97/07301, filed April 11, 1997 (WO 97/38729); each incorporated herein by reference for this purpose.

Please amend the paragraph on page 98, line 22 as follows:

U.S. Application Serial No. 08/662,341, filed June 12, 1996, now U.S. Patent No. 6,143,037, and PCT Application Serial No. PCT/US97/10079, filed June 11, 1997 (WO 97/47254), are also each specifically incorporated herein by reference without disclaimer for the purposes of describing the preparation and use of coated medical devices as part of a gene transfer protocol for DNA delivery to bone repair cells. The devices described can be effectively used with the aspects of this invention that concern gene delivery to bone cells and tissues.

Please amend the paragraph on page 99, line 3 as follows:

Matrix-mediated gene transfer has also been employed to create transfected cells that constitutively express recombinant hPTH1-34 *in vivo* and to stimulate bone formation (fully described in U.S. Application Serial No. 08/199,780, filed February 18, 1994, now U.S. Patent No. 5,763,416, incorporated herein by reference for this purpose).

Please amend the paragraph on page 99, line 16 as follows:

As described in U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 5,962,427, and PCT Application Serial No. PCT/US97/07301, filed April 11, 1997 (WO 97/38729), each incorporated herein by reference for this purpose, there is a clinical need to stimulate scar formation during the repair of soft tissues in order to enhance the mechanical competence of the injured tissue.

Please amend the paragraph on page 101, line 1 as follows:

Each of U.S. Application Serial No. 08/662,341, filed June 12, 1996, now U.S. Patent No. 6,143,037, and PCT Application Serial No. PCT/US97/10079, filed June 11, 1997 (WO 97/47254), are specifically incorporated herein by reference without disclaimer for the purposes of describing the preparation and use of coated medical devices. Such devices can be used to advantage in combination with the present invention to facilitate repair of soft tissues, *e.g.*, after injury.

Please amend the paragraph on page 101, line 9 as follows:

As also described in U.S. Application Serial No. 08/631,334, filed April 12, 1996, now U.S. Patent No. 5,962,427, and PCT Application Serial No. PCT/US97/07301, filed April 11, 1997 (WO 97/38729), each incorporated herein by reference for this purpose, there is a clinical need to prevent excessive fibrosis (restenosis), as may occur during blood vessel repair following angioplasty. This can be accomplished by the delivery of genes that encode lysyl oxidase inhibitors, or by transfer of genes that encode certain TGF-βs. There is, in addition, a clinical need to regulate angiogenesis, *e.g.*, in vascular insufficiency disorders, where the goal is to stimulate new vessel formation in order to prevent tissue hypoxia and cell death.

Please amend the paragraph on page 102, line 21 as follows:

U.S. Application Serial No. 08/662,341, filed June 12, 1996, now U.S. Patent No. 6,143,037, and PCT Application Serial No. PCT/US97/10079, filed June 11, 1997 (WO

97/47254), are also each specifically incorporated herein by reference without disclaimer for the purposes of describing the preparation and use of coated medical devices for therapeutic intervention connected with blood vessels. Such devices can be advantageously used with those aspects of the present invention that concern gene delivery to blood vessels.

Please amend the paragraph on page 103, line 5 as follows:

U.S. Provisional Application Serial No. 60/042,198, filed March 31, 1997, the priority document for U.S. Patent Nos. 6,281,256 and 6,797,738 and WO 98/44027, PCT Application No. PCT/US98/06188 (WO 98/44027), filed March 31, 1998 and designating the U.S. and U.S. Patent Application Serial No. 09/402,119, filed September 20, 1999, now U.S. Patent No. 6,281,256, are each specifically incorporated herein by reference without disclaimer for the purpose of even more fully describing controlled and open pore matrix preparation. In the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated. All parts and percentages are by weight.

Please amend the paragraph on page 108, line 22 as follows:

As described in U.S. Provisional Application Serial No. 60/042,198, filed March 31, 1997, the priority document for U.S. Patent Nos. 6,281,256 and 6,797,738 and WO 98/44027, specifically incorporated herein by reference without disclaimer, the ability of the GF/PL matrices to allow cell adhesion and tissue formation was demonstrated in *in vitro* studies. SMCs adhered to the GF/PL matrix and covered the available surface area following seeding. A significant increase in cell number was noted after 2 wk in culture. The average cell density was 1.71×10^7 cells/mL and 3.05×10^7 cells/mL at 0 and 2 wk, respectively. This is a 43.8% increase in cell density.

Please amend the paragraph on page 117, line 29 as follows:

Each of U.S. Provisional Application Serial No. 60/026,362, filed September 19, 1996, the priority document for U.S. Patent No. 6,642,363; U.S. Provisional Application Serial No. 60/026,467, the priority document for U.S. Patent No. 6,642,363, filed September 19, 1996; U.S. Provisional Application Serial No. 60/041,565, the priority document for U.S. Patent No. 6,642,363, filed March 21, 1997 and PCT Application Serial PCT/US97/16890, filed September 19, 1997 (WO 98/12228) are specifically incorporated herein by reference without disclaimer for the purposes of describing the preparation and use of further unique polymeric materials and matrices thereof.

Please amend the paragraph on page 121, line 2 as follows:

U.S. Provisional Application Serial No. 60/128,681, filed April 09, 1999, now U.S. Patent No. 6,511,650, is specifically incorporated herein by reference without disclaimer for the purposes of describing the preparation and use of further unique polymeric materials and matrices thereof. In particular, this application teaches the preparation and use of porous hydrogel materials formed by first creating gas pockets in the gel and then removing the gas to create a material with an open, interconnected pore structure that is maintained over extended time periods and has high mechanical integrity.